A METHOD TO IMPUTE TIME TO KIDNEY TRANSPLANT OUTCOMES IN THE PRESENCE OF PREVALENT EVENTS IN THE CHRONIC KIDNEY DISEASE IN CHILDREN (CKID) COHORT

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ABSTRACT

Kidney transplant outcomes may be determined as the time at which glomerular filtration rate (GFR) <45 ml/min|1.73m2, as an indicator of poor transplant prognosis. We aimed to characterize these outcomes after transplant in the Chronic Kidney Disease in Children (CKiD) cohort. For a substantial proportion of children, their first GFR was observed to be below 45 ml/min and this occurred at heterogeneous times after transplant. Using data from 143 children who received a transplant and contributed GFR data, for 24 the time when GFR<45 ml/min was determined by interpolation between two observations above and below this threshold; 18 had a first GFR<45 ml/min and were classified as prevalent events and the remaining 101 participants contributed GFR>45 ml/min. To impute times for the prevalent events, we used a two-stage model approach that may be applied to other settings in which trajectories of biomarkers define events. The first model aimed to determine level of GFR shortly after transplantation (0.25 years) using empirical Bayes estimates of the intercept and slope from linear mixed models with GFR as the dependent variable and time as the independent variable among children who contributed GFR data within 1 year after transplantation. The empirical Bayes estimates provided the estimated levels of GFR at 0.25 years after transplant. Using these data as the outcome and pre-transplant variables as the predictors, we then constructed an imputation model to determine GFR levels among prevalent cases. For 18 prevalent cases, the time when GFR<45ml/min was interpolated from the imputed value at 0.25 years

and the first observed GFR<45ml/min. This proposed approach used a combination of observed data, empirical Bayes estimates and imputed values to estimate time to event for all individuals and was less biased compared to a simple cumulative incidence approach which does not account for heterogeneous follow-up time.

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PREFACE

Kidney transplant has become the preferred treatment modality for end-stage renal disease (ESRD) among children during the last decade. Therefore, determining risk factors prior to ESRD that are related to poor pediatric kidney transplant outcome is an area of high priority. To address this important research question in clinical cohorts, a valid study endpoint for middle to long-term pediatric kidney transplant outcome is crucial. Based on previous studies, kidney transplant outcome can be determined as the time at which glomerular filtration rate (eGFR) below a clinically meaningful threshold value, as an indicator of poor transplant prognosis in epidemiological studies. In this study, we aimed to characterize an outcome of time to low eGFR event by imputing an starting value after transplant in the Chronic Kidney Disease in Children (CKiD) cohort, in order to resolve the methodological challenge due to heterogeneous follow-up time.

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INTRODUCTION

Kidney transplant has become the preferred treatment modality for end-stage renal disease (ESRD) among children, adolescents and young adults during the last decade based on USRDS data. Between 2010-2014, 36% of children with ESRD received a kidney transplant within the first year of medical care (1). In addition, approximately 800 renal transplants are performed in children below 18 years of age annually in the United States (2). Therefore, determining factors prior to ESRD that are related to poor kidney transplant outcome in children is an area of high priority. To better address this research topic, a study endpoint that can well represent the risk of having poor transplant outcome will be of importance.

Renal graft failure defined as either re-transplantation or return to dialysis has been commonly used as the primary measure of poor kidney transplant outcome in previous studies. However, renal graft failure may not be able to detect the risk of having unfavorable outcome in a preemptive manner so that intervention could be applied earlier. A recent study has shown that estimated glomerular filtration rate (eGFR) calculated by a serum creatinine-based formula performed well in measuring post-transplant kidney function in children having received a kidney transplant (3). Additionally, it has been shown that post-transplant renal function measured by serum creatinine can predict long-term renal graft failure among adults (4). Based on these findings, we think a measure for middle-to-long-term pediatric kidney transplant

outcome determined by a serum creatinine-based eGFR level would be helpful as a research endpoint in pediatric chronic kidney disease (CKD) research.

In this study, we seek to characterize the kidney transplant outcome in children by using time from initiation of transplant to a low eGFR event that was defined based on a threshold value of 45 ml/min|1.73 m^2. However, in cohort studies where eGFR values are longitudinally collected at follow-up visits that occurred at heterogeneous time after transplant, some participants may be first observed an eGFR below the threshold. These participants are referred as having a prevalent event and would have been excluded from further analysis. The Chronic Kidney Disease in Children (CKiD) study is well positioned to address this methodological challenge. It is a prospective cohort aimed at investigating pediatric CKD progression. In the original CKiD cohort, detailed phenotyping data before kidney transplant was well collected by close follow-up visits. However, post-transplant data collection was not initiated until a later time, by which a proportion of existing participants had already received transplant for a substantial period of time and developed a prevalent event. To resolve this practical problem that might also be seen in other cohorts, our study proposed a method to impute the missing eGFR levels the study failed to capture at an earlier time after transplant, and to estimate time to the low eGFR event in the presence of prevalent events with the help of these imputed values.

METHODS

Study design and participants

The Chronic Kidney Disease in Children (CKiD) Study is a multicenter, prospective cohort study conducted at 54 pediatric nephrology centers across North America with the primary aim to determine risk factors for decline in renal function and progression of chronic kidney disease (CKD) in children. Details of the CKiD design have been previously published (3). Briefly, eligible children were between 1 and 16 years with mild to moderate CKD based on an estimated GFR of 30-90 mL/min/1.73 m^2 (9). Regular study visits occurred annually until the initiation of renal replacement therapy (RRT, dialysis or kidney transplant). At regular visits, data were collected on kidney function, cardiovascular health, neurocognitive development, growth, and self-reported medical history and socioeconomic factors. Regular visits ceased after documented initiation of RRT but participants could participate in short study visits in which self-reported general health, eGFR levels and clinical events were collected by telephone or in-person (PIP) interviews. The study protocol was approved by the institutional review board of each participating center, and participants and their families provided informed consent. From January 2005 through December 2015, a total of 891 participants were enrolled in CKiD study. The present analysis was limited to participants who received kidney transplant and had at least one PIP follow-up after transplant (N=155).

Time to event outcome

To better characterize poor kidney transplant prognosis based on a meaningful threshold value of GFR, we suggested a time to event outcome that could account for the length of time from transplant to the first occurrence of a low eGFR value.

The outcome of interest was time from the initiation of kidney transplantation to the date when eGFR < 45 ml/min|1.73 m^2. Previous studies have shown that eGFR is a valid measure of kidney function in pediatric kidney transplant recipients (1), though it may be unstable shortly after the initiation of transplantation. Thus, we anchor the time origin at 0.25 years after transplant in order to allow for a period of GFR stabilization. Observed eGFR < 45 ml/min|1.73m^2 within 0.25 years after transplant was not considered as an indication of poor transplant outcome because it may be highly variable between individuals and measurements due to delayed allograft function (8), human leukocyte antigen (HLA) compatibility (10), acute rejection (8), type of kidney (7), or medical center factors (2). The eGFR levels after transplant were obtained by PIP interviews using self- or parent-reported information from the most recent clinical examination. A validated equation derived from CKiD population was used to estimate these GFR values based on serum creatinine, cystatin C, blood urea nitrogen, height and gender (9). As a measure of poor transplant prognosis and one of secondary outcomes in CKiD study, this time to event outcome may not be directly captured by the irregular PIP visits after

transplant. Thus, we only observed a period during which the eGFR trajectory declined to a level below 45 ml/min|1.73m^2 among those individuals having the poor transplant prognosis. More importantly, 42% (n=18) of all children with poor transplant prognosis had their first eGFR observation after transplant below 45 ml/min due to a delayed PIP interview. They were referred as having prevalent events since we could only observe a partial trajectory of post-transplant eGFR after they had already developed the low eGFR event. For children with prevalent event, at least another eGFR value before their first post-transplant eGFR observation was needed in order to determine their event time. Therefore, we were going to impute a starting value of eGFR shortly after they had received kidney transplant and then estimate the event time based on this imputed value.

Pre-transplant variables

The pre-transplant variables that were used to estimate the time to event outcome including age, race, primary CKD diagnosis, eGFR level, annualized eGFR ratio, urine protein-creatinine ratio (uP/C), BMI, height, and socioeconomic status (SES) at study enrollment. CKD diagnosis was dichotomized as either having an underlying glomerular or non-glomerular cause (11). eGFR levels were longitudinally collected at each regular visit from study enrollment until the initiation of kidney transplantation using the same validated CKiD eGFR equation (9), but based on standardized laboratory

measurements. The annualized eGFR ratio, as a metric of kidney function decline, was defined as $\frac{GFR_{v_i}/GFR_{V_{i-1}}}{time_{v_i} - time_{v_{i-1}}}$, where time was in years. Specifically, we fitted individual-specific linear regressions where time from study enrollment was the predictor and log eGFR was the dependent variable using eGFR values across all time points prior to transplant (6). Urine protein and creatinine were measured centrally in the laboratory at University of Rochester (12). BMI and height Z-scores were standardized by age and gender from the normal population. Participants and their parents were asked to report household income level, maternal education status (having vs. not having a college degree), medical insurance types (private vs. public), and whether they had received social worker or food assistance in the past 12 months, as a proxy of socioeconomic status.

Statistical analysis

Since the low eGFR event was determined by the threshold limit of 45 ml/min|1.73m^2, the methodological problem was that of prevalent events (i.e., first post-transplant eGFR observation < 45 ml/min) into the cohort. We sought to develop a method to impute the eGFR starting value at 0.25 years after transplant so that the prevalent events can be included as informative cases in our analysis. The proposed method includes three steps.

Step 1: linear mixed effects model and empirical Bayes estimates

The first model aimed to determine level of eGFR at 0.25 years after transplant using the empirical Bayes estimates for each individual. To obtain the empirical Bayes estimates, we applied a linear mixed effects model, which allowed for random intercepts and slopes of eGFR over time to deviate from the population means among children who contributed eGFR data within 1 year from transplant. We centered time at 0.25 years from transplant so that the empirical Bayes estimate of intercept could be easily converted to the eGFR starting value. Specifically, this model was of the form:

$$\log(eGFR)_{ij} = (\alpha + a_i) + (\beta + b_i) * time_{ij} + \varepsilon_{ij}$$

where $$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}\right] \qquad \varepsilon_{ij} \sim N(0, \sigma^2)$$

Here, we use α and β to denote the population intercept and slope, respectively. In the equation, a_i and b_i are the random intercept and slope, respectively, for the ith individual. The ε_{ij} is the Gaussian error term for the jth observation of the ith individual. Time in the model was specified to be anchored at 0.25 years after transplant. The covariance matrix was modeled to be unstructured. After fitting the mixed liner model, we used the *predict* command with the *reffects* option in Stata to obtain the empirical Bayes estimates of individual intercept. Lastly, we took the exponential of this value and obtained the eGFR starting value at 0.25 years after transplant. However, the eGFR starting value imputed by empirical Bayes estimates were only available for those children who have at least one eGFR observation within 1 year from transplant.

Step 2: multivariate linear regression model with pre-transplant variables as predictors

For children who had no eGFR observation within 1 year from transplant but contributed data at some later time, a multivariate linear regression (MLR) model was used to impute their eGFR level at 0.25 years after transplant. The MLR model was informed by the empirical Bayes estimates and the pre-transplant variables at study enrollment including age, race, CKD diagnosis, log-transformed eGFR level, annualized eGFR ratio, log-transformed uP/C, BMI Z-score, height Z-score, and socioeconomic status. Specifically, we estimated the parameters of the MLR model where the log-transformed eGFR starting value obtained in step 1 was the dependent variable and pre-transplant variables were predictors. We then took the expected value of log(eGFR) at 0.25 years for a given profile of predictors as the best estimation and then transformed the value back to arithmetic scale. Therefore, for children without eGFR observation within 1 year from transplant, their eGFR starting values were imputed by MLR model.

Step 3: Determine time from transplant to the low eGFR (< 45 ml/min|1.73m^2) event

We assumed a linear relationship within each adjacent pair of eGFR values, and used the combination of imputed and observed values to interpolate the time at which eGFR < 45 ml/min. The time of prevalent event was interpolated based on the imputed eGFR starting value and the first eGFR observation. The

time of incident event (i.e., having at least one observation before the first observed eGFR below 45 ml/min) was imputed based on two observed data points between which the event occurred. Children who had no observed eGFR < 45 ml/min were censored at their last visit. We excluded children whose imputed eGFR starting value at 0.25 years was less than 45 ml/min because they were not at risk for our event of interest.

We described the imputed eGFR starting values stratified by imputation methods, as well as the median and interquartile range of estimated event times. The estimated time to low eGFR event, as a measure of poor kidney transplant outcome, was graphically presented by the Kaplan-Meier survival curves with 95% confidence bands. We also compared the 25^{th} percentile and 50^{th} percentile of event times among population including (N=143) versus excluding (N=125) the prevalent events. All analyses were conducted using STATA/SE 13.1 (Statacorp LP) and SAS 9.4 (SAS Institute, Inc.). Graphic figures were constructed using R statistical software 3.1.2 (R Foundation for Statistical Computing) and STATA/SE 13.1 (Statacorp LP).

RESULTS

Of 891 children enrolled in CKiD, 192 children received a kidney transplant. Of these, 155 children had at least one estimated GFR observation after transplant. Table 1 presents the descriptive statistics of pre-transplant demographic, clinical, growth and socioeconomic characteristics of these 155 children at study enrollment. The median age at transplant was 15 years. Most children were diagnosed with non-glomerular CKD (72%). The median estimated GFR was 36.5 ml/min|1.73 m^2 and over two thirds of the study population had either elevated or nephrotic proteinuria at study enrollment. In addition, these 155 children had on average lower height and weight compared to normal population; 68% had a maternal education less than college degree and 40% were from low-income families.

Among 155 children who contributed eGFR observations after transplant, 3 children only had one GFR observation within 0.25 years from receiving a transplant. They were excluded in the further analysis because eGFR level within this short time after transplant may be unstable and not predictive of long-term outcomes. Table 2 shows the length of time from transplant to the first eGFR observation collected. For those children whose first observed eGFR was greater than 45 ml/min, the median time from transplant to the first observation was 0.9 years. Among children with the first observed eGFR less than or equal to 45 ml/min, median time after transplant at which this first eGFR was collected was 2.7 years. This delayed post-transplant visit lead to a

missing data problem. In other words, it was very likely that because the longer period between transplant and the PIP visit allowed time for kidney function to deteriorate, we observed a low eGFR as the first available record. If we could capture eGFR data earlier, we might observe a higher value before the first available record. To address this missing data problem, we used a linear mixed effects model (step 1) and MLR (step 2) to impute a starting eGFR value at 0.25 years after transplant.

In step 1, the linear mixed effect model was performed on 80 children contributing a total of 90 eGFR observations within 1 year from transplant. Table 3 presents the data and parameter estimates for the linear mixed effect model. When we centered time at 0.25 years after transplant, the intercept of the linear mixed effect model with log(eGFR) as the dependent variables was 4.03. This intercept corresponds to a population average eGFR level of 56.3 ml/min at 0.25 years after transplant. The slope of the same mixed effects model was 0.12 (95%CI: -0.06, 0.31), which suggests that on average, the eGFR was 13% higher one year after receiving transplant among these 80 children (13%=(exp(0.12)-1)*100%). For the remaining 72 children, we used MLR model with pre-transplant variables as predictors to impute their eGFR starting values (i.e., eGFR at 0.25 years after transplant) in step 2. Table 4 shows the parameter estimates for the MLR model.

After we obtained the eGFR starting values for each individual, we summarized and compared the descriptive statistics of these imputed values between two

imputation methods (Table 5). The medians of imputed eGFR at 0.25 years after transplant were similar between empirical Bayes estimates and MLR model, both at about 58 ml/min. The eGFR starting values imputed by empirical Bayes estimates have a wider interquartile range comparing to those imputed by MLR, however the difference was minimal.

In step 3, we classified individuals into four categories based on the patterns of eGFR trajectory: 1) incident event, 2) prevalent event, 3) censored, and 4) excluded. We then applied a category-specific approach to estimate their time to low eGFR event or censoring.

Category 1: Incident event (n=24)

We defined the incident event as having at least one observation before a first observed eGFR that was less than 45 ml/min. In our study population, 24 children (17%) were classified as having an incident event. Figure 1 shows the post-transplant eGFR trajectories of 5 children as examples. For these children, their event times were determined by assuming a linear relationship between two adjacent eGFR observations, one was above 45 min/ml, and the other was below. In figure 1.1, there were 6 eGFR observations and an imputed staring value for the example child. Of all observed values, one was within 0.25 years from transplant and five were after. Coincidentally, the fourth observation after 0.25 years from transplant was collected at a level very close to the threshold of 45 ml/min. Thus, the estimated event time was similar to the time at which the fourth observation was collected. However, for children in

figure 1.2 and figure 1.4, the interpolation yielded more accurate estimations of event time comparing to only using the observed times.

Category 2: Prevalent event (n=18)

We defined the prevalent event as having the first post-transplant eGFR observation less than 45 ml/min. Notably, 42% of events defined as eGFR < 45 ml/min and 13% of participants in our study population had a prevalent event. Figure 2 shows 5 examples of eGFR trajectories for children having prevalent event. The event times were interpolated by the imputed eGFR starting value and the first eGFR observation after transplant. The starting values were either imputed by empirical Bayes estimates (figure 2.1 and 2.2) or by multiple linear regression model (figure 2.3 through 2.5). Most of imputed starting values were consistent with the overall linear trend characterized by later observed values, regardless of the imputation method was used. In figure 2.3, the first eGFR observation after transplant was just slightly less than the threshold value of 45 ml/min, and its trajectory increased later. In this case, our estimation may not be as accurate as in figure 2.4 and figure 2.5. However, the prevalent events would have been excluded if the starting value was not imputed, which could lead to a huge loss in statistical power due to limited numbers of events.

Category 3: Censored (n=101)

There were 101 children (71%) who never experienced an eGFR less than 45 ml/min during PIP follow-ups after transplant, and thus were censored at their last visit. As shown in figure 3.2 and figure 3.5, some of participants were only

followed for one or two years, and then had loss to follow-up. It was possible that they developed events later, though we had not been able to capture them. If we only used cumulative incidence counts as the outcome, they would have been classified as not having event, which might biased further analysis. By censoring them at the last visit, we take the person-time contributed by these children into account and maximize the use of available information.

Category 4: Excluded (n=9)

We excluded 9 children (6%) whose imputed eGFR starting value at 0.25 years after transplant was less than or equal to 45 ml/min|1.73 m^2. Figure 4 shows the trajectories of 5 children as examples. Because the outcome of interest was defined based on an eGFR threshold value of 45 ml/min, children with an imputed starting value less than 45 ml/min were not considered as being at risk of the event. Although some of children's eGFR had increased to a level greater than the threshold and had a recurrent low eGFR afterward (for example, figure 4.5), they did not contribute person time in this analysis.

Table 6 presents the medians and interquartile ranges of time from transplant to the low eGFR event or censoring that were estimated by proposed method. Overall, half of events occurred before 2.4 years after transplant and half of non-events were censored before 2.8 years after transplant. Based on our method, the median of estimated time when eGFR declined to a level less than 45 ml/min was earlier among children having prevalent event (1.2 years, IQR: [0.7, 2.8]) than among children having incident event (2.5 years, IQR: [1.8,

3.6]). The earlier times among prevalent events may reflect a systematic difference in disease severity. It was likely that children with prevalent events tend to be sicker and need intensive care, which prevented them from being accessed by telephone contacts. However, we cannot exclude the possibility that our methods tend to underestimate the prevalent event time (i.e., define an earlier event time than if multiple eGFR values were observed leading up to it) because of the linear interpolation between two data points.

Figure 5a presents the Kaplan-Meier curve and the 95% confidence band among 143 children included in our analysis. The estimated time at which 25% and 50% of population had experienced a low eGFR event based on proposed method were 3.1 and 6.6 years after transplant, respectively. In contrast, if we performed a naïve analysis and excluded prevalent events (n=125), the time at which 25% population had experienced an eGFR< 45 ml/min would have been 4.2 years and the median would have been unspecified due to limited number of events.

The data structure is now set up to investigate putative risk factors for time to eGFR < 45 ml/min after a kidney transplant in order to identify modifiable variables and improve pediatric transplant prognosis.

DISCUSSION

Glomerular filtration rate (GFR) is a biomarker that has been widely used in epidemiological studies related to pediatric nephrology. Multiple formulas for calculating eGFR have been developed and validated in different setting (14). In this study, we used the eGFR values calculated by the CKiD 2012 equation. This serum creatinine-based equation has been shown to perform well in measuring post-transplant kidney function at measured GFR < 90 ml/min|1.73 m^2 among pediatric kidney transplant recipients (3). Based on the KIDGO 2012 Clinical Practice Guideline (15), GFR < 45 ml/min|1.73 m^2 was suggested to be used as the threshold value to classify mildly to moderately decreased kidney function (Stage G3a) as this level is related to substantially increased risk in kidney failure, cardiovascular mortality, and acute kidney injury. The present study defined the low GFR event as the first occurrence of an observed eGFR < 45 ml/min after transplant to assess poor kidney transplant outcome. Comparing to other approaches that may require intensive clinical or laboratory examinations, this low eGFR event is more feasible to be applied in large cohort studies as a surrogate for poor transplant outcome and a potential clinically relevant endpoint prior to graft failure.

When defining the occurrence of a clinical event based on a threshold value of a biomarker in longitudinal studies, missing values in some repeated measurements of the biomarker may prevent us from observing the exact event time. In the CKiD cohort, the first post-transplant eGFR values were obtained

at heterogeneous times. For children whose post-transplant PIP visits occurred well after transplant, their first eGFR observations after transplant tended to be lower. This was likely due to the longer time period from transplant to the PIP visit had allowed us to observe the deterioration of their kidney function after a temporary improvement resulting from transplant. In addition, as the secondary outcome, post-transplant kidney function was collected mainly by telephone contact. For children with worse kidney function after having transplant, they may need intensive care during which we could not reach them by phone calls. Therefore, the missing data that should have been collected at scheduled PIP visits created an absence of data at a critical time. This resulted in a substantial proportion of children in the cohort were observed having a prevalent event.

To resolve this methodological problem, we proposed an approach to determine the low eGFR event time using a combination of observed data and imputed starting values obtained by empirical Bayes techniques or multivariate linear regression. Empirical Bayes estimates derived from linear mixed effects models are conventional tools for characterizing linear trajectories of biomarkers measured repeatedly over time in individuals. It was obtained by the relative weighting of the individual eGFR observations collected during PIP visits, and the population means of eGFR trajectory that were informed by the parameter values of mixed effects model. As the eGFR level may change over time after having transplant, we restricted to observations within one year from transplant to build the linear mixed effects model, with the aim of estimating

eGFR starting value. However, most children who contributed observations to the mixed effects model had only a single data point during the one-year time window. Taking the advantage of empirical Bayes estimates, child-specific slopes can be estimated as closely linked to the population average slope, which allowed us to impute their eGFR starting value at 0.25 years after transplant without introducing external information. For children having no eGFR observations during the one-year time window, we used pre-transplant information to impute their eGFR starting values. It is worth mentioning that although these imputed starting values are informed by pre-transplant factors, they are still valid to be used as a component for constructing the time to event outcome in studies where these pre-transplant factors may also serve as exposures of interest. Since the event time is mainly determined by later eGFR observations, investigating the relationship between this time to event outcome and the pre-transplant factors that are both the exposures, and at the same time, involved in the imputation process are assumed to be valid.

There were several advantages to using the time to low eGFR event estimated by proposed method as a measure of poor kidney transplant outcome in cohort studies. First, it allowed us to maximize the data by imputing an eGFR starting value for children with prevalent event and including them in further analysis. It is crucial to maximize the data and increase statistical power since the pediatric kidney transplant is a relatively rare condition. Second, compared to using a cumulative incidence approach as the measure of poor kidney transplant outcome, the time to low eGFR event avoids summarizing post-

transplant eGFRs collected at heterogeneous times across individuals into a homogeneous binary variable. Here, the poor transplant outcome is defined by eGFR level that may change over time, and children with longer follow-up time after transplant were more likely to observe an eGFR < 45 ml/min. The proposed method properly accounts for the loss to follow-up in the longitudinal study design and maximize the available information by including time as a component for measuring poor kidney transplant outcome. Based on this outcome, a wide range of survival analysis techniques can be easily applied. Lastly, although this method was motivated by the methodological challenge we have encountered in the context of pediatric transplant, it can be also generalized to other settings in which thresholds of biomarkers define events and prevalent events are common due to heterogeneous follow-up time. The length of time window that were used to impute starting values, the time origin at which events were anchored to ensure stable biomarker levels, and the threshold value for defining the event of interest are all modifiable and can be optimized based on different purposes.

This study had several limitations. First, when building the MLR model to impute the eGFR starting values for children having no eGFR observations within one year from transplant, we used the eGFR starting values obtained by empirical Bayes estimates as the dependent variable. By doing this, we assumed a same relationship between pre-transplant factors and the eGFR starting values among children with and without eGFR observations within one year after transplant. However, this assumption may be violated. In addition,

children having no data during the first year are also likely to be sicker. Therefore, the parameter estimates of the MLR model may be affected by potential selection bias, and will not result in an accurate prediction for the other subset of children. Second, the proposed method may underestimate the event time for prevalent events because of the interpolation using two data points. Figure 1.2 may serve as a good example to illustrate what the estimated event time would have been if we failed to observed the first two data points after transplant. In that case, we would have to interpolate event time use the imputed starting value at 0.25 years and the first eGFR observation below 45 ml/min (i.e., the third observation). And the estimated event time would be around 1 year after transplant instead of 2 years as shown in the graph. Third, we only used a single imputation by the MLR model. The proposed approach can be potentially extended to multiple imputations that can incorporate valid estimation of uncertainty. Lastly, we anchored the event time at 0.25 years after transplant in order to allow enough time for eGFR level after transplant to stabilize. It is possible that pediatric kidney transplant recipients need more time than this for the stabilization of eGFR level. It might be worthy to investigate another time origin in further studies in order to obtain a more robust estimation.

In summary, we suggested a sequential approach to impute eGFR levels shortly after kidney transplant and characterize poor kidney transplant outcome as the time to low eGFR event for pediatric recipients in cohort studies. This provides one possible solution for the missing data problem in repeated measurements

of biomarkers, in which prevalent events determined by a threshold of this biomarker can be included in further analysis. The proposed method can be applied in other settings, and may serve as an initiate template of resolving similar challenges for other epidemiologic questions.

APPENDICES

Table 1. Descriptive statistics of pre-transplant characteristics at study enrollment among children who had at least one estimated GFR observations after transplant (N=155)

	Median [IQR] or % (N)
Demographic characteristics	
Male	63% (97)
Race	
White	67% (104)
Black	20% (31)
Other	13% (20)
Age at transplant (year)	15.0 [12.5, 17.1]
CKD duration at transplant (year)	12.9 [8.8, 16.4]
Time from study entry to transplant (year)	3.7 [1.8, 6.0]
Clinical characteristics	
Non-glomerular CKD diagnosis	72% (112)
Estimated GFR (ml/min|1.73 m^2)	36.5 [30.9, 44.4]
Annual change in eGFR prior to transplant	-15.5% [-25.1%, -8.6%]
Urine protein:creatinine, mg/mg of creatinine	1.2 [0.4, 2.7]
Proteinuria	
Minimal (< 0.2 mg/mg of Cr)	30% (45)
Elevated (0.2 to 2 mg/mg of Cr)	38% (56)
Nephrotic (> 2 mg/mg of Cr)	32% (48)
Uncontrolled hypertension	54% (82)
Growth characteristics	
Abnormal birth history (premature, low birth weight or small gestational age)	27% (39)
Height z-score	-0.8 [-1.7, 0.1]
Weight z-score	-0.2 [-1.2, 0.8]
BMI z-score	0.5 [-0.4, 1.2]
Socioeconomic characteristics	
Maternal education less than college degree	68% (103)
Household income <$36K per year	40% (61)
Food assistance in past year	17% (26)
Any public insurance	47% (69)

Abbreviations: IQR, interquartile range; %, percentage; N, number; GFR, glomerular filtration rate; CKD, chronic kidney disease. Median [IQR] for continuous variables and %(N) for categorical variables. Height, weight, and BMI z-scores were based on the normal population and standardized by age and gender.

Table 2. Time of eGFR values observed from transplantation stratified by first eGFR observation greater or less than 45 ml/min/1.73 m², median [IQR]

	1st observed eGFR > 45 (N=125)	1st observed eGFR <= 45 (N=27)
Time from transplant to 1st eGFR observation, yr	0.91 [0.48, 2.14]	2.70 [0.71, 3.51]
Time from transplant to last eGFR observation, yr	3.19 [1.84, 5.78]	4.13 [1.84, 6.57]

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; N, number; yr, years after transplant

Table 3. Data and parameters for linear mixed model among children having eGFR observations within 1 years after transplant, (95% CI)

Number of subjects	80
Number of observations in total	90
Number of children contributed	
One observation	71
Two observations	8
Three observations	1
Population intercept (log scale, centered)	4.03 (3.94, 4.13)
Average eGFR level at 0.25 years after transplant, ml/min	56.3 (51.4, 62.2)
Population slope (log scale, difference per year)	0.12 (-0.06, 0.31)
Average percent of eGFR increase per year	13% (-6%, 36%)
SD of random intercepts	0.34 (0.27, 0.42)
SD of random slopes	0.52 (0.35, 0.76)
Correlation of random intercept and slope	-0.80 (-0.90, -0.61)
SD of residuals	0.02 (0.01, 0.08)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation. Time was centered at 0.25 years after transplant. The average eGFR level was converted from population intercept, and the average percent of eGFR increase was obtained by population slope.

Table 4. Parameter estimates for pre-transplant variables in multivariate regression model [1]	
Pre-transplant variables	**Coefficient (95% CI)**
Age at transplant, year	-0.04 (-0.06, -0.02)
White race	0.17 (0.03, 0.30)
Glomerular CKD diagnosis	0.22 (0.06, 0.38)
Log eGFR level at study enrollment, ml/min|1.73 m^2	0.29 (-0.01, 0.59)
Annual change in eGFR prior to transplant	0.32 (-0.15, 0.78)
Log urine protein:creatinine, mg/mg of creatinine	0.02 (-0.03, 0.07)
BMI z-score, standardized by age and gender	0.01 (-0.05, 0.06)
Height z-score, standardized by age and gender	0.02 (-0.03, 0.07)
Maternal education higher than college	-0.02 (-0.15, 0.11)
Any public insurance	0.09 (-0.05, 0.23)
Social worker assistance	-0.16 (-0.30, -0.03)

[1] Model was fitted using data from 80 children who contributed eGFR observations within 1 year after transplant. The coefficients were used to predict eGFR starting values for 72 children who have no eGFR observations within 1 year. The dependent variable was log-transformed eGFR starting value.

Table 5. Descriptive statistics of imputed eGFR level at 0.25 years after transplant by imputation methods			
	Empirical Bayes Estimate [a]	**Imputed from MLR [b]**	**Overall**
Number (%)	80 (53.5)	72 (46.5)	152
Median	57.8	57.7	57.7
[IQR]	[49.9, 66.7]	[50.1, 65.3]	[50.1, 66.3]

Abbreviations: eGFR, estimated glomerular filtration rate; MLR, multivariate linear regression; IQR, interquartile range. [a] Restricted to children contributed eGFR in the first year after transplant. [b] Restricted to children who have no eGFR observations within the first year after transplant.

Table 6. Descriptive statistics of time from initiation of transplantation to eGFR < 45 ml/min|1.73 m² or censoring, year		
	N	**Median [IQR]**
Overall event (eGFR < 45 ml/min)	42	2.4 [1.2, 3.6]
Incident event	24	2.5 [1.8, 4.2]
Prevalent event	18	1.2 [0.7, 2.8]
Censored	101	2.8 [1.7, 4.7]

Abbreviations: eGFR, estimated glomerular filtration rate; N, number; IQR, interquartile range

Type 1: Incident event (n=24)

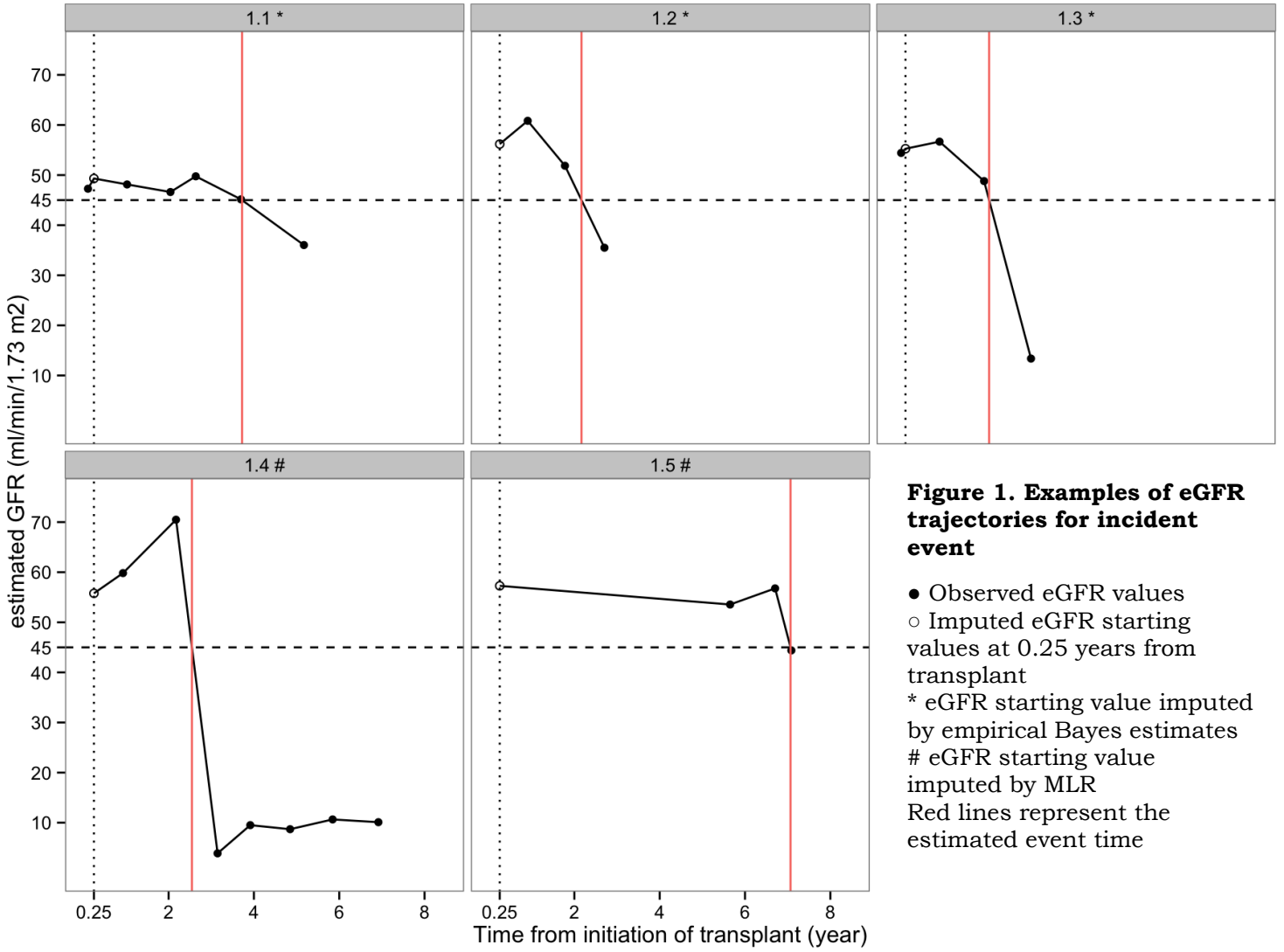


Figure 1. Examples of eGFR trajectories for incident event

● Observed eGFR values
○ Imputed eGFR starting values at 0.25 years from transplant
* eGFR starting value imputed by empirical Bayes estimates
# eGFR starting value imputed by MLR
Red lines represent the estimated event time

Type 2: Prevalent event (n=18)

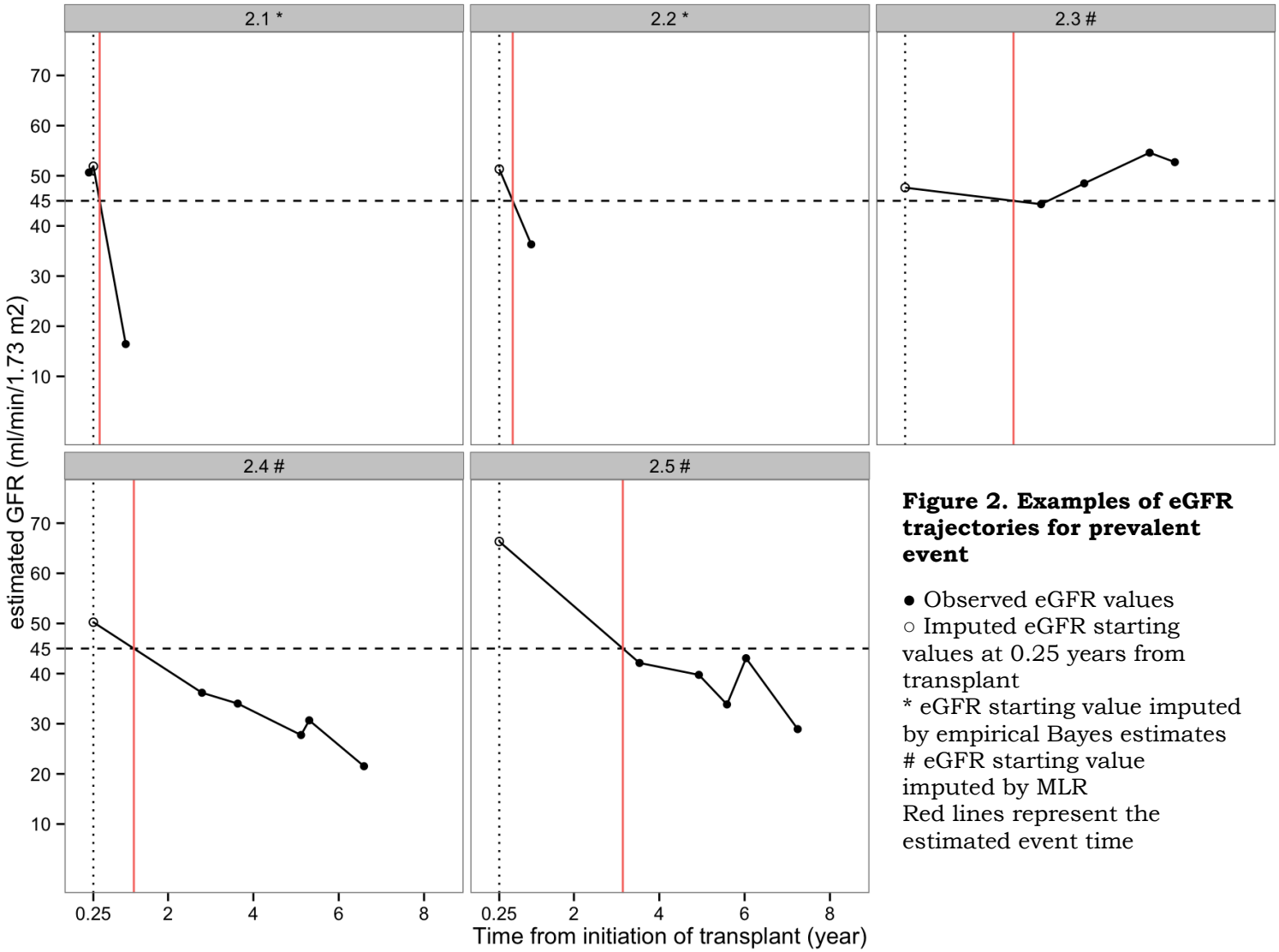


Figure 2. Examples of eGFR trajectories for prevalent event

● Observed eGFR values
○ Imputed eGFR starting values at 0.25 years from transplant
* eGFR starting value imputed by empirical Bayes estimates
# eGFR starting value imputed by MLR
Red lines represent the estimated event time

Type 3: Censored (n=101)

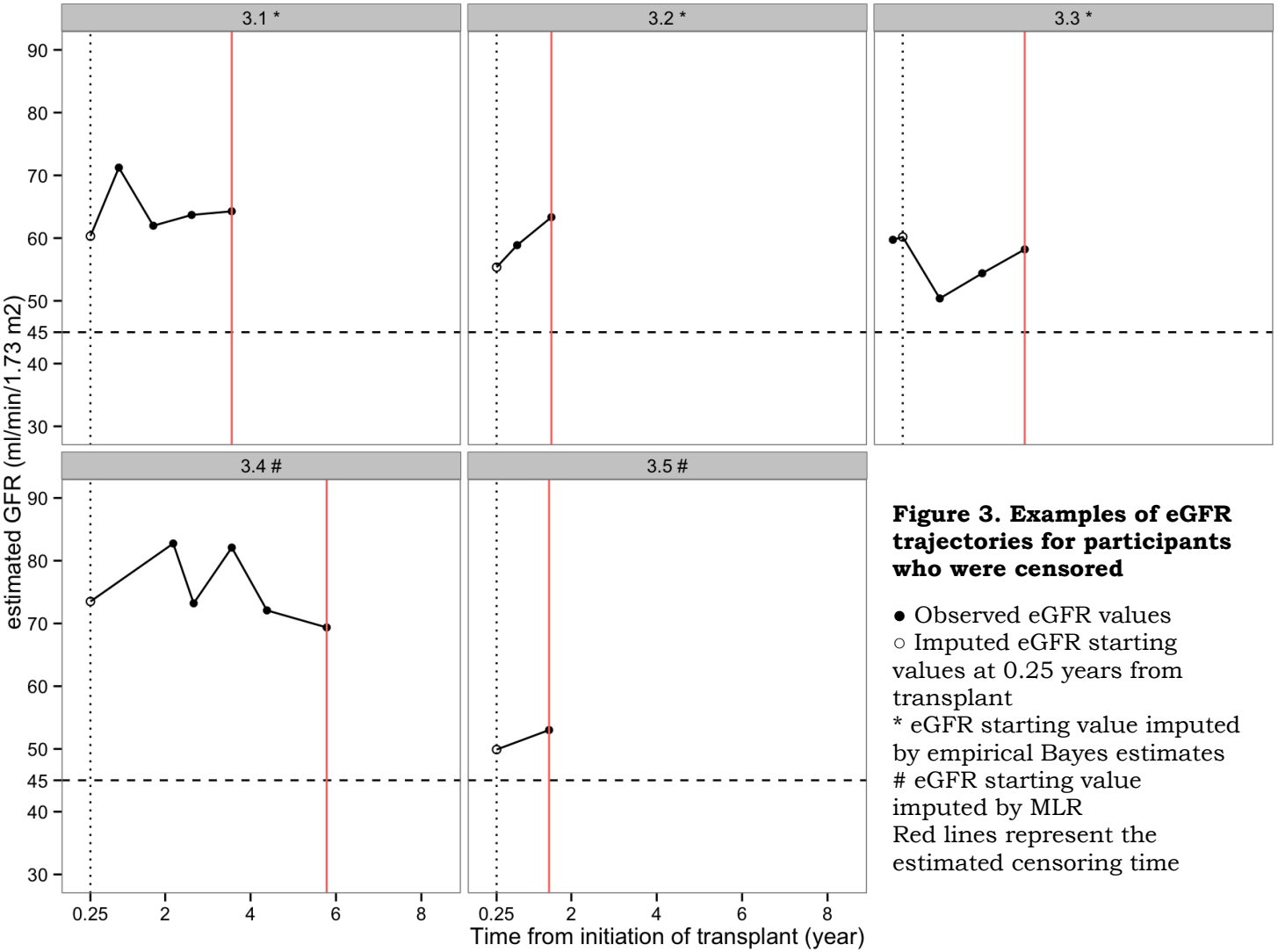


Figure 3. Examples of eGFR trajectories for participants who were censored

● Observed eGFR values
○ Imputed eGFR starting values at 0.25 years from transplant
* eGFR starting value imputed by empirical Bayes estimates
# eGFR starting value imputed by MLR
Red lines represent the estimated censoring time

Type 4: Excluded (n=9)

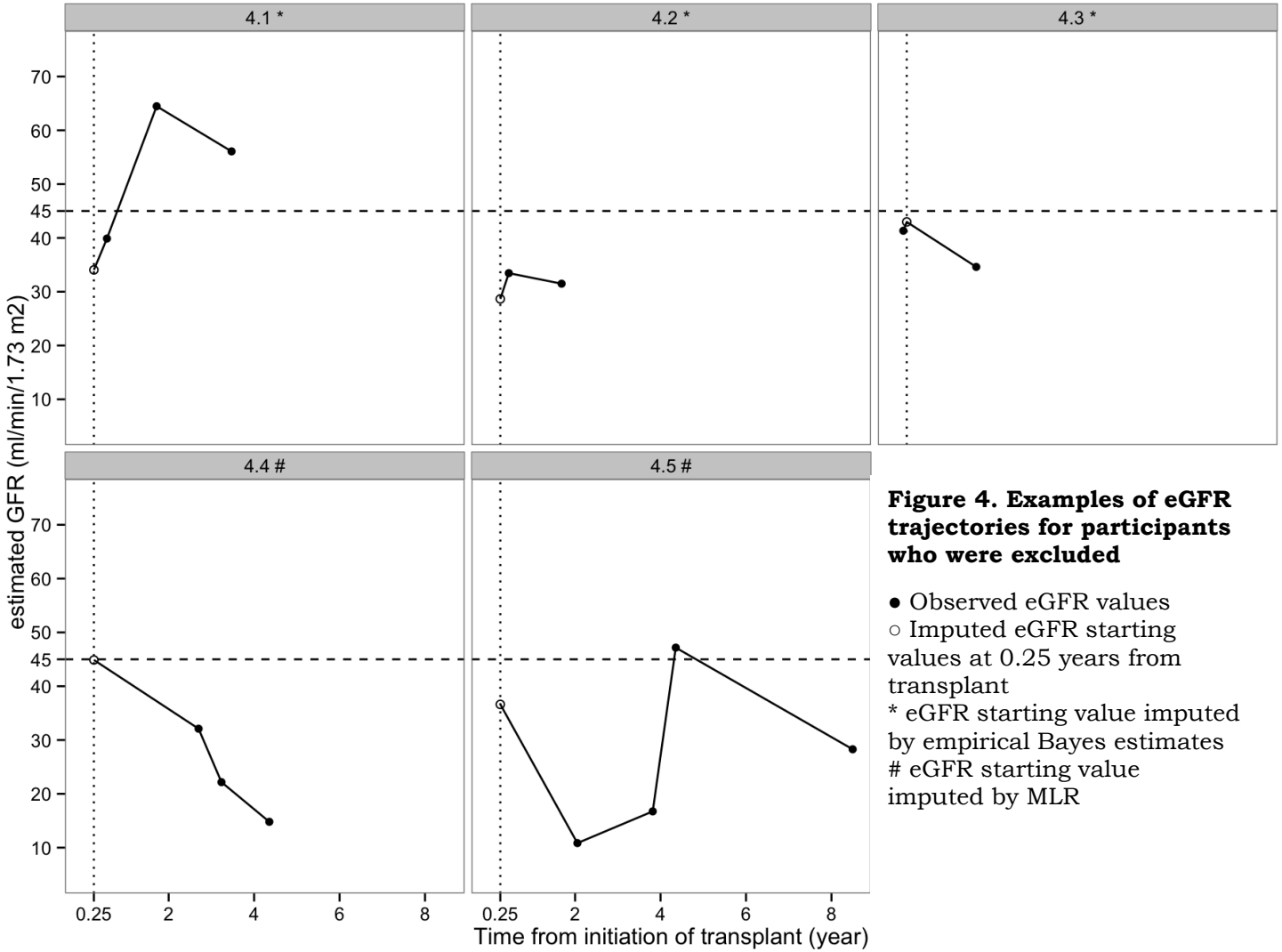
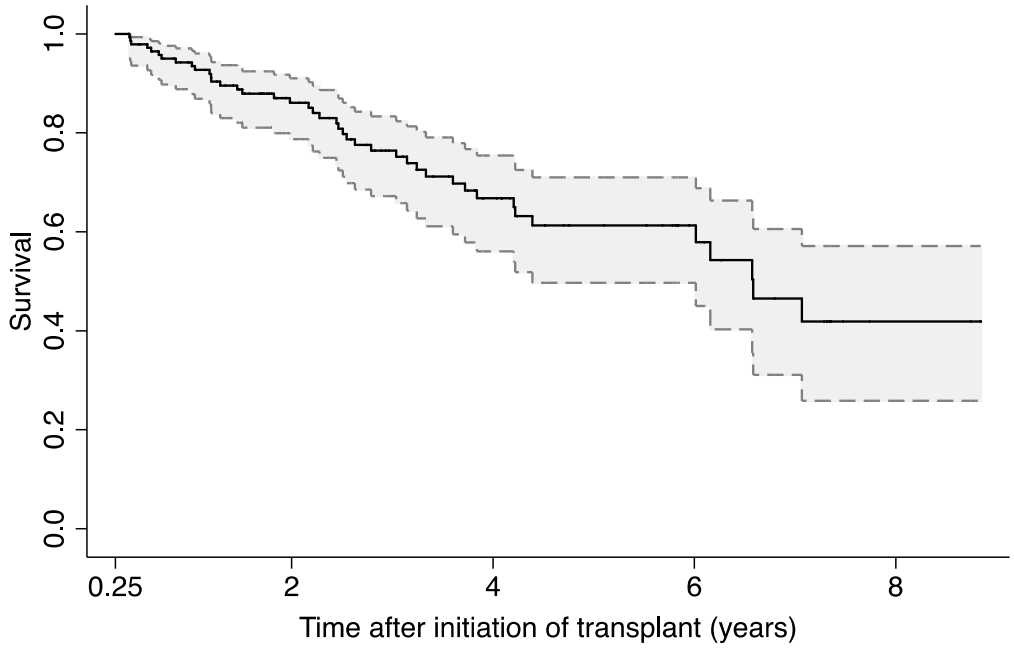


Figure 4. Examples of eGFR trajectories for participants who were excluded

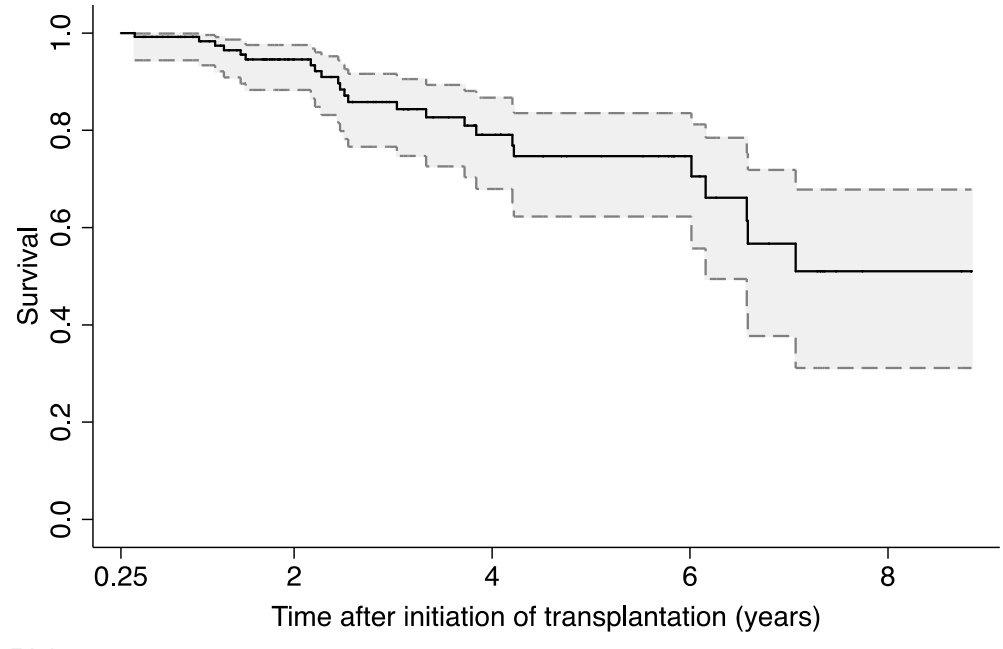
● Observed eGFR values
○ Imputed eGFR starting values at 0.25 years from transplant
* eGFR starting value imputed by empirical Bayes estimates
# eGFR starting value imputed by MLR



N at Risk:

143	87	41	18	3

Figure 5a. Kaplan-Meier survival curve (95%CI) for low eGFR event



N at Risk:

125	81	40	18	3

Figure 5b. Kaplan-Meier survival curve (95%CI) for low eGFR event

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CURRICULUM VITAE

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PROFILE

Master of Science (ScM) degree candidate specializing in epidemiology with a strong focus towards child health. Student investigator with experience in longitudinal data analysis, survival analysis and statistical machine learning.

EDUCATION

Master of Science (ScM), GPA: 4.00/4.00 Expected May 2017
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Track: General Epidemiology and Methodology
Master's Thesis: A method to impute time to low GFR after kidney transplant in the presence of prevalent events in the Chronic Kidney Disease in Children Cohort

Bachelor of Management, GPA: 3.98/4.00 July 2015
Zhejiang University, Hangzhou, China
Major: Fitness and Health Management
Bachelor's Thesis: Effect of outdoor air pollution and related physical education policy on the change of physical activity pattern among elementary school students

RESEARCH EXPERIENCE

Research Assistant, Maternal factors during pregnancy in prediction of childhood obesity among Latino children, Johns Hopkins School of Medicine, Baltimore, MD

Jan. 2017 - Current

- Applied statistical techniques to translate clinical data from the Boston Birth Cohort (BBC) into a clinical tool to predict future obesity risk during childhood among low-income Latino children

- Externally validate the childhood obesity risk score using data from the Children's Medical Practice (CMP) cohort
- Supervised by Dr. Sarah Polk (JHSOM), Prof. Alvaro Muñoz (JHSPH)

Research Assistant, Chronic Kidney Disease in Children (CKiD) Study, Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD

June 2016 – Jan. 2017

Association of kidney function after renal transplant with pre-transplant characteristics among children with chronic kidney disease (CKD)

- Explored the pattern of kidney function after transplant and defined the clinically unfavorable post-transplant outcome based on estimated glomerular filtration rate
- Described the association of post-transplant kidney function with pre-transplant characteristics including CKD progression, cardiovascular, growth and socioeconomic factors
- Results have been included in The Kidney Disease in Children Data Management and Analysis Center (KIDMAC) 2017 Annual Report

Self-reported antihypertensive medication adherence and renal replacement therapy among children with chronic kidney disease (CKD)

- Examined the association of self-reported ACE inhibitors and ARBs adherence with time to renal replacement therapy among children with CKD by using Cox model with a time-varying HR to account for non-proportionality
- Performed competing risk analysis for dialysis and transplant by comparing sub-distribution cumulative incidence functions across adherence groups
- Results have been presented in KIDMAC group meeting

Household income as a mediator of the effect of maternal education on post-transplant kidney function among children with chronic kidney disease (CKD)

- Applied the counterfactual approaches to mediation analysis that allow for exposure-mediator interaction to estimate controlled direct effect (CDE), natural direct effect (NDE) and natural indirect effect (NIE) of maternal education

- Compared the results of traditional mediation analysis with the counterfactual approaches and assessed the magnitude of exposure-mediator interaction
- Results have been presented in the General Epidemiology and Methodology Research in Progress (GEM-RIP) Meeting

Master's Thesis, advised by Dr. Derek Ng

Sept. 2016 – May 2017

A method to impute time to low GFR after kidney transplant in the presence of prevalent events in the Chronic Kidney Disease in Children Cohort

- Used linear mixed effect model, empirical Bayes estimates and multivariate linear regression to impute eGFR missing values caused by heterogeneous follow-up time and incomplete data collection after kidney transplantation
- Proposed a sequential approach to estimate time to low eGFR event as a measure of poor kidney transplant outcome by using a combination of observed and imputed eGFR values
- Abstract has been accepted by the 50th Annual Meeting of the Society for Epidemiologic Research (SER) and the 30th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research (SPER) for poster presentation; Poster has been presented in 2017 Delta Omega Poster Competition; manuscript is being prepared for submission

COURSE PROJECT

Statistical Machine Learning: Methods, Theory, and Applications

Feb. – April. 2017

Prediction of mortality status and age at examination in NHANES 2003-2004 survey data

- Conducted data management and data cleaning for large data set (n=10122)
- Performed feature selection and dimensionality reduction among 813 potential predictors to train regression and classification models
- Algorithms used to predict age including least square with forward/backward selection, tree-based regression (random forest, bagging, gradient boosting model), shrinkage techniques (Lasso, ridge regression)

- Algorithms used to predict mortality status including linear discriminant analysis, classification trees, support vector machine with linear/polynomial/radial kernel
- Best-preformed models were selected based on cross-validation

Advanced Methods for Design and Analysis of Cohort Studies

Sept. – Nov. 2016

Association of baseline household income level with progression of chronic kidney disease: an examination of the Chronic Kidney Disease in Children Study

- Described the association of baseline income level with eGFR rate of change using mixed linear models, stratified by CKD (glomerular/non-glomerular) diagnosis
- Applied the joint model with Weibull distribution to account for informative dropout due to renal replacement therapy
- Explored the interaction of maternal education and baseline income by CKD diagnosis

Methodological Challenge in Epidemiologic Research

April – June 2016

Clinical diagnosis of depression and risk of cognitive impairment in the Baltimore Memory Study

- Investigated the association between depression status and cognitive change among middle-aged and elder population by using propensity score-matched, multiple linear and logistic regressions

ACTIVITIES/HONORS

Medhacks 2.0, medical hackathon held by Johns Hopkins University

Sept. 2016

Method and techniques for the early detection of acute kidney injury

- Defined and validated two indicators for kidney stress, urine output resistivity and urine output inadequacy, based on oxygen perfusion, optimal cerebral blood pressure level, and real-time surveillance data of urine output collected by the new device called Renalert during cardiac bypass surgery
- Collaborated with researchers from bioengineering and computer science

Honors from Master's: Charlotte Ferencz Scholarship (March 2017), was nominated to Delta Omega Public Health Honor Society (March 2017)

Honors from Bachelor's: National Scholarship (September 2012 – July 2013), First-class Merit Student Award (2012 - 2015), Outstanding Undergraduate Student (July 2015)

TEACHING EXPERIENCE

Teaching Assistant, Department of Epidemiology, JHSPH, Baltimore, MD

Epidemiologic Inference in Public Health II Nov. – Dec. 2016
Statistical Methods in Public Health IV Mar. 2017 – Current

INTERNSHIP EXPERIENCE

Intern, Institute for Communicable Disease and Prevention, Center for Disease Control and Prevention, Tianjin, China May – Sept. 2014

- Performed the data analysis for the *Risk Factors for Acquisition of Measles Study,* aiming to examine the association of demographic factors, dwelling environment, and immunization situation with acquisition of measles in Chinese rural population
- Conducted Hand-foot-mouth disease outbreak investigation in local kindergartens

PROFESSIONAL DEVELOPMENT

Computer Skills: R programming; SAS; STATA; Mplus; Working knowledge of statistical machine learning

Language Skills: English (fluent), Mandarin (native)

Relevant graduate level coursework:
Epidemiologic Methods I, II, III; Methodologic Challenges in Epidemiologic Research; Advanced Methods for Design and Analysis of Cohort Studies; Statistical Machine Learning; Survival Analysis; Causal Inference in Public Health; Statistics for Psychosocial Research (I, II); Genetic Epidemiology; Statistics for Genomics; Multilevel Statistical Models in Public Health